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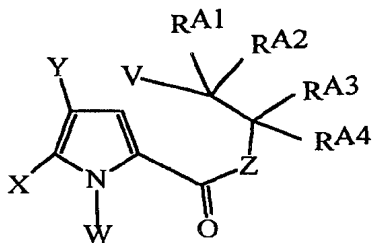
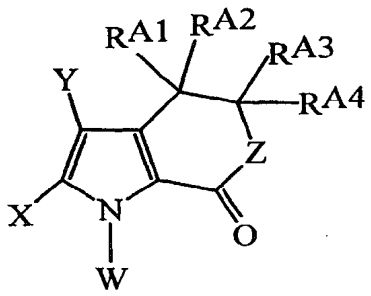


(I)



(II)

(57) Abstract

The present invention relates to methods for preparing a variety of Lamellarin compounds and analogues via a synthetic intermediate, which methods involved the step of performing an intramolecular cyclization of a compound of Formula (I) to produce compounds of Formula (II), wherein the variables are given in the specification.

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Syntheses of a variety of Lamellarin compounds and analagoues

TECHNICAL FIELD

The present invention is generally directed to intermediates useful in the preparation of compounds useful in therapy. More specifically, the present invention relates to intermediates useful in the preparation of a class of fused polycyclic alkaloids. The invention also relates to methods for the preparation of the fused polycyclic alkaloids and their analogues and derivatives.

BACKGROUND ART

Naturally occurring molecules which exhibit potentially beneficial pharmacological properties are isolable from a range of environments, such as marine, plant and microbial sources. One example of such molecules is the general class of compounds known as the Lamellarins. These polyaromatic alkaloids are isolated from marine sources and comprise a fused framework. Lamellarins C and D have been shown to cause inhibition of cell division in fertilised sea urchin assay, whereas Lamellarins I, K and L all exhibit comparable and significant cytoxicity against P388 and A549 cell lines in culture. Recently, Lamellarin N has been shown to exhibit activity in lung cancer cell lines by acting as a Type IV microtubule poison. Furthermore, these compounds have also been shown to possess cytotoxic activity on multidrug resistant cells as well as efficacy as non-toxic modulators of the multidrug resistant phenotype and, therefore, afford an attractive potential source of chemotherapeutic agents.

However, the potential clinical usefulness of the Lamellarins is severely limited by the modest quantities produced naturally as well as the difficulties involved in their isolation.

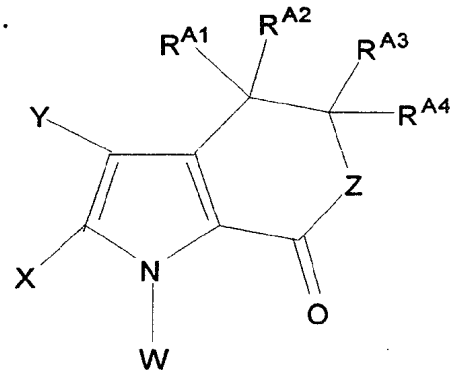
There has accordingly, been significant activity directed towards the development of a synthetic route to this class of molecules, and approaches to these molecules have included

a sequential double cyclization of a 1,3,4-triaryl-2,5-dicarboxysubstituted pyrrole ring (Steglich *et al*, *Angew., Chem. Int. Ed. Eng.* 1997, **36**, 155), and N-ylide-mediated pyrrole ring formation to install the pyrrole and lactone portions of the molecule (Banwell *et al, Chem. Commun.*, 1997, 2259) Ishibashi *et al*, *Tetrahedron*, 1997, **53**, 5951).

The present invention now provides an alternative method via a synthetic intermediate, which allows for the incorporation of a range of substitution patterns and potentially permits access to a variety of Lamellarin compounds and analogues containing the fused polycyclic-pyrrole core.

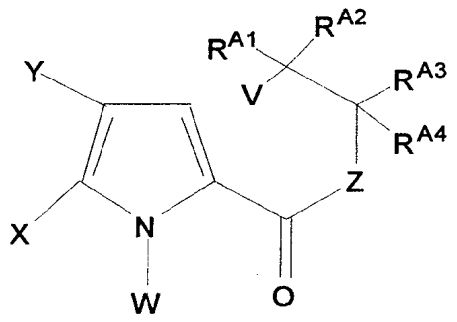
DISCLOSURE OF THE INVENTION

Accordingly, in a first aspect the invention relates to a method for the preparation of a compound of Formula (II).



(II)

comprising the step performing an intramolecular cyclization of a compound of Formula (I):



(I)

wherein:

R^{A1-A4} are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted

alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano; or

R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic group; or

R^{A2} and R^{A3}, together with the carbon atoms to which they are attached form an optionally substituted saturated or unsaturated carbocyclic or heterocyclic group; or

$R^{A1}R^{A2}C\text{-}CR^{A3}R^{A4}$ forms an optionally substituted aryl group or aromatic heterocyclic group;

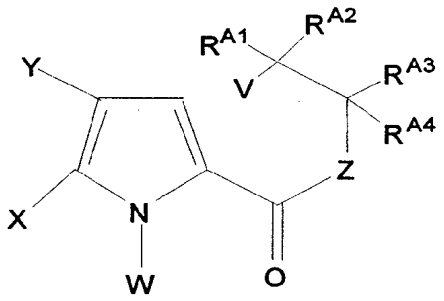
Y is selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano;

W and X are as defined for Y, or together with the nitrogen and carbon atoms to which they are attached, form a saturated or unsaturated nitrogen containing heterocyclic group which may be optionally substituted or optionally fused to a saturated or unsaturated carbocyclic group, aryl group or heterocyclic group;

V represents a halogen or hydrogen atom;

Z is $-(CH_2)_n\text{-}U\text{-}(CH_2)_o-$ where U is selected from CH_2, NH or a heteroatom, and n and o are independently selected from 0, 1, 2 or 3.

In a second aspect, the present invention provides an intermediate compound useful in the preparation of compounds of Formula (II), wherein said intermediate is of Formula (I):



(I)

wherein:

R^{A1-A4} are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano; or

R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic group; or

R^{A2} and R^{A3}, together with the carbon atoms to which they are attached form an optionally substituted saturated or unsaturated carbocyclic or heterocyclic group; or

$R^{A1}R^{A2}C\text{-}CR^{A3}R^{A4}$ forms an optionally substituted aryl group or aromatic heterocyclic group;

Y is selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano;

W and X are as defined for Y, or together with the nitrogen and carbon atoms to which they are attached, form a saturated or unsaturated nitrogen containing heterocyclic group which may be optionally substituted or optionally fused to a saturated or unsaturated carbocyclic group, aryl group or heterocyclic group;

V represents a halogen or hydrogen atom;

Z is $-(CH_2)_n-U-(CH_2)_o-$ where U is selected from CH_2, NH or a heteroatom, and n and o are independently selected from 0, 1, 2 or 3.

Yet a further aspect of the present invention relates to compounds of Formula (II) as defined above, prepared by the methods described herein.

As used herein the term "alkyl", denotes straight chain, branched or cyclic fully saturated hydrocarbon residues. Unless the number of carbon atoms is specified the term preferably refers to C_{1-20} alkyl or cycloalkyl. Examples of straight chain and branched alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethyl-propyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2,-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, 5-methoxyhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethyl-pentyl, 1,2,3,-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, 6-methylheptyl, 1-methylheptyl, 1,1,3,3-tetramethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-methyl-octyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-, 2- or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-, 3- or 4-propylheptyl, undecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-ethylnonyl, 1-, 2-, 3-, 4- or 5-propylocytl, 1-, 2- or 3-butylheptyl, 1-pentylhexyl, dodecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-, 5- or 6-propylnonyl, 1-, 2-, 3- or 4-butyloctyl, 1-2-pentylheptyl and the like. Examples of cyclic alkyl include mono- or polycyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.

As used herein the term "alkenyl" denotes groups formed from straight chain, branched or cyclic hydrocarbon residues containing at least one carbon-carbon double bond including

ethylenically mono-, di- or poly-unsaturated alkyl or cycloalkyl groups as previously defined. Unless the number of carbon atoms is specified the term preferably refers to C_{1-20} alkenyl. Examples of alkenyl include vinyl, allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1-4,pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

As used herein the term "alkynyl" denotes groups formed from straight chain, branched or cyclic hydrocarbon residues containing at least one carbon-carbon triple bond including ethynically mono-, di- or poly- unsaturated alkyl or cycloalkyl groups as previously defined. Unless the number of carbon atoms is specified the term preferably refers to C_{1-20} alkynyl. Examples include ethynyl, 1-propynyl, 2-propynyl, and butynyl isomers, and pentynyl isomers.

The terms "alkoxy, "alkenoxy and "alkynoxy respectively denote alkyl, alkenyl and alkynyl groups as hereinbefore defined when linked by oxygen.

The term "halogen" denotes fluorine, chlorine, bromine or iodine.

The term "aryl" denotes single, polynuclear, conjugated and fused residues of aromatic hydrocarbon ring systems. Examples of aryl include phenyl, biphenyl, terphenyl, quaterphenyl, naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl, pyrenyl, idenyl, azulenyl, chrysenyl.

The term "heterocyclic" denotes mono- or polycarbocyclic groups, including aryl, wherein at least one carbon atom is replaced by a heteroatom, preferably selected from nitrogen, sulphur and oxygen. Where the mono- or polycarbocyclic group which has at

least one carbon atom replaced by a heteroatom is an aryl group, this is referred to as a aromatic heterocyclic group.

Suitable heterocyclic groups include N-containing heterocyclic groups, such as,
unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl or tetrazolyl;
saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as, pyrrolidinyl, imidazolidinyl, piperidyl, pyrazolidinyl or piperazinyl;
condensed saturated or unsaturated heterocyclic groups containing 1 to 5 nitrogen atoms, such as, indolyl, isoindolyl, indolinyl, isoindolinyl, indolizinyl, isoindolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, purinyl, quinazolinyl, quinoxalinyl, phenanthradinyl, phenathrolinyl, phthalazinyl, naphthyridinyl, cinnolinyl, pteridinyl, perimidinyl or tetrazolopyridazinyl;
saturated 3 to 6-membered heteromonocyclic groups containing 1 to 3 oxygen atoms, such as tetrahydrofuranyl, tetrahydropyranyl, tetrahydrodioxinyl,
unsaturated 3 to 6-membered hetermonocyclic group containing an oxygen atom, such as, pyranyl, dioxinyl or furyl;
condensed saturated or unsaturated heterocyclic groups containing 1 to 3 oxygen atoms, such as benzofuranyl, chromenyl or xanthenyl;
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms, such as, thienyl or dithiolyl;
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, oxazolyl, oxazolinyl, isoxazolyl, furazanyl or oxadiazolyl;
saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, morpholinyl;
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, benzoxazolyl or benzoxadiazolyl;
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolyl, thiazolinyl or thiadiazoyl;
saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1

to 3 nitrogen atoms, such as, thiazolidinyl; and
unsaturated condensed heterocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, benzothiazolyl or benzothiadiazolyl.

The term "acyl" refers to a carboxylic acid residue wherein the OH is replaced with a residue, for example, as defined for W, X, and Y and specifically may denote carbamoyl, aliphatic acyl group or acyl group containing an aromatic ring, which is referred to as aromatic acyl or a heterocyclic ring, which is referred to as heterocyclic acyl, preferably C_{1-20} acyl. Examples of suitable acyl include carbamoyl; straight chain or branched alkanoyl such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl and icosanoyl; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl and heptyloxycarbonyl; cycloalkylcarbonyl such as cyclopropylcarbonyl cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl; alkylsulfonyl such as methylsulfonyl and ethylsulfonyl; alkoxysulfonyl such as methoxysulfonyl and ethoxysulfonyl; aroyl such as benzoyl, toluoyl and naphthoyl; aralkanoyl such as phenylalkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutylyl, phenylpentanoyl and phenylhexanoyl) and naphthylalkanoyl (e.g. naphthylacetyl, naphthylpropanoyl and naphthylbutanoyl]; aralkenoyl such as phenylalkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl and phenylhexenoyl and naphthylalkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl and naphthylpentenoyl); aralkoxycarbonyl such as phenylalkoxycarbonyl (e.g. benzyloxycarbonyl); aryloxycarbonyl such as phenoxycarbonyl and napthyloxycarbonyl; aryloxyalkanoyl such as phenoxyacetyl and phenoxypropionyl; arylcarbamoyl such as phenylcarbamoyl; arylthiocarbamoyl such as phenylthiocarbamoyl; arylglyoxyloyl such as phenylglyoxyloyl and naphthylglyoxyloyl; arylsulfonyl such as phenylsulfonyl and napthylsulfonyl; heterocycliccarbonyl; heterocyclicalkanoyl such as thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl and tetrazolylacetyl; heterocyclicalkenoyl such as heterocyclicpropenoyl, heterocyclicbutenoyl,

heterocyclicpentenoyl and heterocyclichexenoyl; and heterocyclicglyoxyloyl such as thiazolylglyoxyloyl and thienylglyoxyloyl.

The term "acyloxy" refers to acyl, as herein before defined, when linked by oxygen.

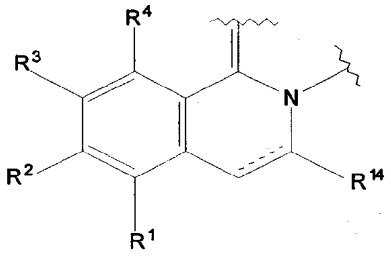
In this specification "optionally substituted" is taken to mean that a group may or may not be further substituted or fused (so as to form a condensed polycyclic group) with one or more groups selected from alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, hydroxy, alkoxy, alkenyloxy, aryloxy, benzyloxy, haloalkoxy, haloalkenyloxy, haloaryloxy, nitro, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylamino, diarylamino, benzylamino, dibenzylamino, acyl, alkenylacyl, alkynylacyl, arylacyl, acylamino, diacylamino, acyloxy, alkylsulphonyloxy, arylsulphenyloxy, heterocyclyl, heterocycloxy, heterocyclamino, haloheterocyclyl, alkylsulphenyl, arylsulphenyl, carboalkoxy, carboaryloxy mercapto, alkylthio, benzylthio, acylthio, cyano, nitro , sulfate and phosphate groups. The term "optionally protected" is taken to mean that a group such as a hydroxy group may or may not be protected by a protecting group. Suitable protecting groups are known and examples thereof are described in *Protective Groups in Organic Synthesis*, by T.W. Greene, (1981), John Wiley & Son.

As used herein, "heteroatom" refers to any atom other than a carbon atom which may be a member of a cyclic organic compound. Examples of suitable heteroatoms include nitrogen, oxygen, sulfur, phosphorous, boron, silicon, arsenic, sellenium and telluruim, especially nitrogen, oxygen and sulfur.

In preferred embodiments of compounds of Formulae (I) and (II), U, as defined in Z, is selected from one of CH_2, NH, oxygen or sulfur. More preferably U is NH or oxygen. Most preferably, U is oxygen. In another preferred embodiment of Z, n + o =0, 1, 2, 3 or 4. Suitable examples of Z include -O-CH_2-, -CH_2-N-, -O-CH_2-O-, -$(CH_2)_3$-, -CH_2-NH-CH_2- or -CH_2-O-CH_2-. In another preferred embodiment, n and o are both zero.

In another preferred form, V is hydrogen, iodine or bromine.

In other embodiments of Formulae (I) and (II), when W and X, together with the nitrogen and carbon atoms to which they are attached, form a saturated or unsaturated heterocyclic group, the group is preferably optionally substituted quinolinyl, optionally substituted isoquinolinyl, optionally substituted dihydroquinolinyl, optionally substituted dihydroisoquinolinyl, optionally substituted pyridyl or dihydro or tetrahydro congeners thereof, or optionally substituted phenanthridine. Preferably, W and X together with the nitrogen and carbon atoms to which they are attached, form an optionally substituted isoquinolinyl or optionally substituted dihydroisoquinolinyl group of general Formula (i):



(i)

wherein R^1 - R^4 and R^{14} are as defined for Y above, and ----- represents an optional double bond.

Preferably R^1 - R^4 of Formula (i) are hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester, wherein the ester is preferably methyl, ethyl, propyl or butyl ester; optionally substituted amino,; carboxamido, wherein the nitrogen atom thereof is optionally substituted by one or two alkyl groups independently selected from methyl, ethyl, propyl or butyl; or sulfate. Most preferably they are hydrogen, hydroxy, methoxy, ethoxy, iso-propoxy, methyl, ethyl, propyl, acetoxy or sulfate. Preferably R^{14} is hydrogen or hydroxy.

In yet other embodiments of Compounds of Formulae (I) and (II), when $R^{A1}R^{A2}C$-$CR^{A3}R^{A4}$ form an aryl group or an aromatic heterocyclic group, it may be an optionally substituted benzene or naphthalene ring or an optionally substituted aromatic heterocyclic

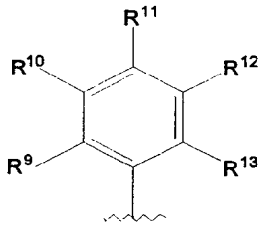
group such as pyridine, furan, pyrrole or thiophene and benzene-fused analogues thereof, for example, quinoline, indole, benzofuran and benzothiophene. Attachment of the bicyclic heterocyclic group may be via the benzene or heterocyclic ring. Preferably $R^{A1}R^{A2}C\text{-}CR^{A3}R^{A4}$ forms an optionally substituted benzene group. Preferably the substituents are hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester, wherein the ester is preferably methyl, ethyl, propyl or butyl ester; optionally substituted amino,; carboxamido, wherein the nitrogen atom thereof is optionally substituted by one or two alkyl groups independently selected from methyl, ethyl, propyl or butyl; or sulfate. Most preferably they are hydrogen, hydroxy, methoxy, ethoxy, iso-propoxy, methyl, ethyl, propyl, acetoxy or sulfate.

In another embodiment $R^{A1\text{-}A4}$ are preferably independently selected from hydrogen, optionally substituted alkyl, optionally protected hydroxy, optionally substituted alkoxy, optionally substituted phenyl or acyloxy. In one preferred embodiment, at least one of R^{A1} or R^{A3} may be hydrogen. In another embodiment, both R^{A1} and R^{A3} are hydrogen. In yet a further emodiment, three or four of $R^{A1\text{-}A4}$ are hydrogen.

In another embodiment, when R^{A2} and R^{A3} together form a bond so as to form a group $R^{A1}C{=}CR^{A4}$, R^{A1} and R^{A4} each may be independently selected from hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester, wherein the ester is preferably methyl, ethyl, propyl or butyl ester; optionally substituted amin or; carboxamido, wherein the nitrogen atom thereof is optionally substituted by one or two alkyl groups independently selected from methyl, ethyl, propyl or butyl. In especially preferred forms, one or both of R^{A1} and R^{A4} are hydrogen.

When R^{A2} and R^{A3}, together with the carbons to which they are attached, form a carbocyclic or heterocyclic group as defined above, preferably they form a 3 to 8-membered cyclic group, preferably 5 to 6-membered cyclic group. Preferably they form a cyclopentane, cyclohexane, cyclopentene, cyclohexene, cyclopentadiene, cyclohexadiene, tetrahydrofuran, dihydrofuran, pyrrolidine, pyrroline, pyran, dihydrophyran, tetrahydropyran or piperidene group. Preferably, R^{A1} and R^{A4} are hydrogen.

In still yet a further embodiment, Y is preferably an optionally substituted phenyl group of Formula (ii):

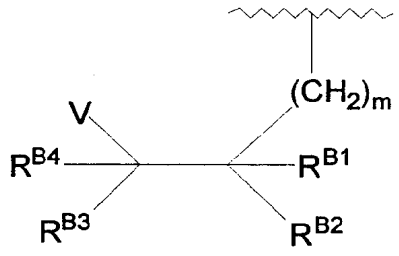


(ii)

Wherein R^9 - R^{13} are as defined for R^1 - R^4 and R^{14} as described above.

More preferably, R^9 - R^{13} are hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester, wherein the ester is preferably methyl, ethyl, propyl or butyl ester; optionally substituted amino,; carboxamido, wherein the nitrogen atom thereof is optionally substituted by one or two alkyl groups independently selected from methyl, ethyl, propyl or butyl; or sulfate. Most preferably, R^9 - R^{13} are selcted from hydrogen, hydroxy, methoxy, ethoxy, iso-propoxy, methyl, ethyl, n-propyl, isopropyl, acetoxy or sulphate.

Another preferred embodiment of Formula (I) is a compound of Formula (Ia) where X is hydrogen and W is a group of the formula (iii);

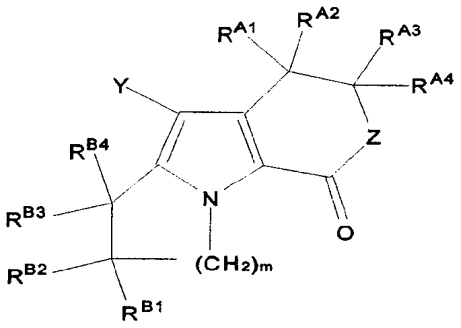


(iii)

wherein V is hydrogen or halogen; R^{B1-B4} are correspondingly defined as for R^{A1-A4} herein above; and

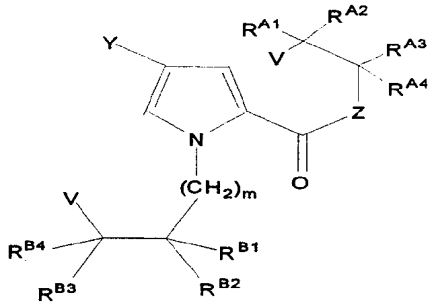
m is selected from 1, 2, 3 or 4.

Thus, in a preferred embodiment, the present invention relates to a method for the preparation of a compound of Formula (IIa):



(IIa)

comprising the step of performing two intramolecular cyclizations on a compound of Formula (Ia):



(Ia)

wherein:

R^{A1-A4} ,V, Y, Z are as defined above;

R^{B1-B4} are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano; or

R^{B2} and R^{B3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic group; or

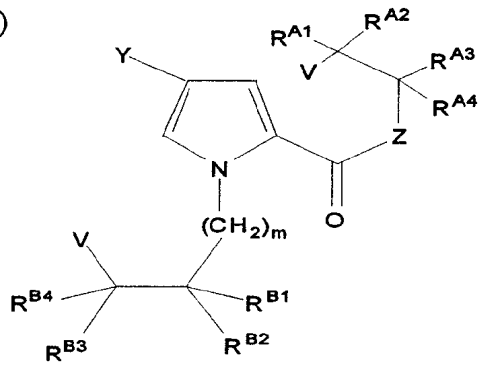
R^{B2} and R^{B3}, together with the carbon atoms to which they are attached form an

optionally substituted saturated or unsaturated carbocyclic or heterocyclic group; or

$R^{B1}R^{B2}C$-$CR^{B3}R^{B4}$ form an optionally substituted aryl group or aromatic heterocyclic group; and

m is selected from 1, 2, 3 or 4.

Another preferred embodiment of the invention provides an intermediate compound of Formula (Ia)



(Ia)

wherein:

R^{A1-A4}, R^{B1-B4}, V, Y, Z and m are as defined above and optionally, one or more (CH_2) groups of $(CH_2)_m$ defined in formula (iii) may be optionally substituted by a group R^{14} as defined above.

In a preferred embodiment m is 1 or 2. Even more preferably m is 2.

In yet other embodiments of Compounds of Formulae (Ia) and (IIa), when $R^{B1}R^{B2}C$-$CR^{B3}R^{B4}$ form an aryl group or an aromatic heterocyclic group, it may be an optionally substituted benzene or naphthalene ring or an optionally substituted aromatic heterocyclic group such as pyridine, furan, pyrrole or thiophene and benzene-fused analogues thereof, for example, quinoline, indole, benzofuran and benzothiophene. Attachment of the bicyclic heterocyclic group may be via the benzene or heterocyclic ring. Preferably $R^{B1}R^{B2}C$-$CR^{B3}R^{B4}$ forms an optionally substituted benzene group. Where $R^{B1}R^{B2}C$-$CR^{B3}R^{B4}$ forms a benzene group (containing the substituent V) cyclization can afford a group of formula (i) as described herein above. Preferably the substituents are hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester, wherein the ester is preferably methyl, ethyl, propyl or butyl ester;

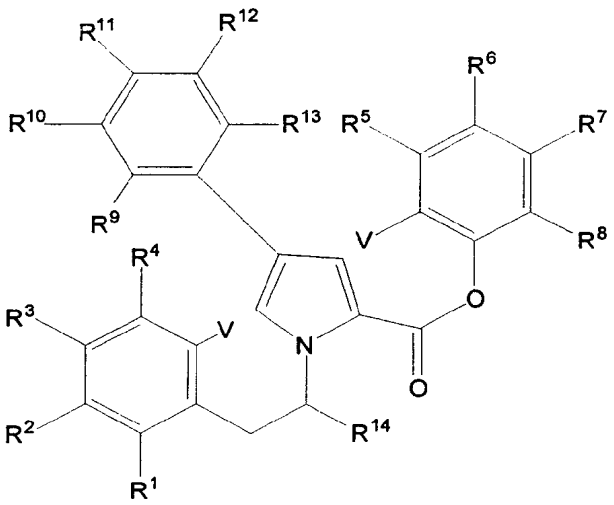
optionally substituted amino,; carboxamido, wherein the nitrogen atom thereof is optionally substituted by one or two alkyl groups independently selected from methyl, ethyl, propyl or butyl; or sulfate. Most preferably they are hydrogen, hydroxy, methoxy, ethoxy, iso-propoxy, methyl, ethyl, propyl, acetoxy or sulfate.

In another embodiment R^{B1-B4} are preferably independently selected from hydrogen, optionally substituted alkyl, optionally protected hydroxy, optionally substituted alkoxy, optionally substituted phenyl or acyloxy. In one preferred embodiment, at least one of R^{B1} or R^{B3} may be hydrogen. In another embodiment, both R^{B1} and R^{B3} are hydrogen. In yet a further emodiment, three or four of R^{B1}-^{B4} are hydrogen.

In another embodiment, when R^{B2} and R^{B3} together form a bond so as to form a group $R^{B1}C=CR^{B4}$, R^{B1} and R^{B4} each may be independently selected from hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester, wherein the ester is preferably methyl, ethyl, propyl or butyl ester; optionally substituted amin or; carboxamido, wherein the nitrogen atom thereof is optionally substituted by one or two alkyl groups independently selected from methyl, ethyl, propyl or butyl. In especially preferred forms, one or both of R^{A1} and R^{A4} are hydrogen.

When R^{B2} and R^{B3}, together with the carbons to which they are attached, form a carbocyclic or heterocyclic group as defined above, preferably they form a 3 to 8-membered cyclic group, preferably 5 to 6-membered cyclic group. Preferably they form a cyclopentane, cyclohexane, cyclopentene, cyclohexene, cyclopentadiene, cyclohexadiene, tetrahydrofuran, dihydrofuran, pyrrolidine, pyrroline, pyran, dihydrophyran, tetrahydropyran or piperidene group. Preferably, R^{B1} and R^{B4} are hydrogen.

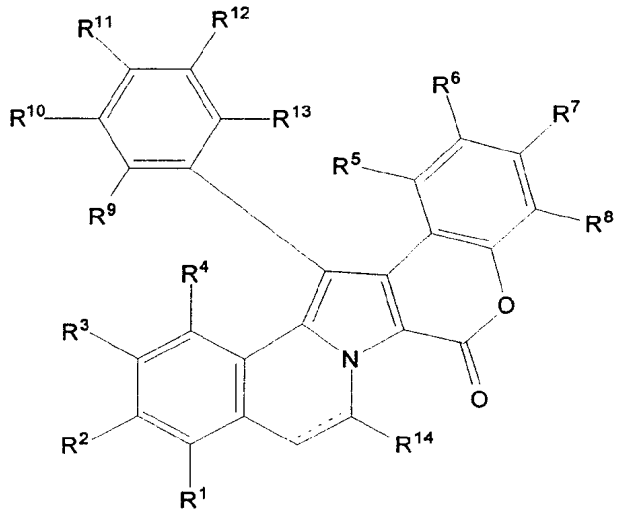
Especially preferred compounds of Formula (I) have the structure of Formula (Ib) below:



(Ib)

where R^1 - R^{14} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyan. Preferred R^1 - R^{14} are selected from hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester, wherein the ester is preferably methyl, ethyl, propyl or butyl ester; optionally substituted amino, such as mono or dialkyl amino; carboxamido, wherein the nitrogen atom thereof is optionally substituted by one or two alkyl groups independently selected from methyl, ethyl, propyl or butyl; or sulfate. More preferably R^1 - R^{13} are selected from hydrogen; hydroxy; optionally substituted alkyl, such as methyl, ethyl or propyl; optionally substituted alkyloxy such as methoxy, ethoxy, n-propoxy, iso-propoxy; acyloxy such as acetoxy; or sulfate and R14 is preferably hudrogen or hydroxy. V is as defined above, preferably hydrogen, iodine or bromine.

Thus a further preferred form of the invention provides a method of preparing a fused polycyclic pyrrole-containing compound of Formula (IIb):



(IIb)

comprising the step of performing two cyclizations on a compound of Formula (Ib).

The intramolecular cyclizations of compounds of Formula (I), preferably of Formula (Ia) or (Ib), to form the polycyclic fused compounds of Formula (II), preferably of Formula (Ia) or (IIb) can be carried out by any suitable means known to those skilled in the art. Suitable methods are described below, however, any other method which will effect the desired cyclization also forms part of the present invention. It will be understood that the groupsV, W, X, Y, Z, R^{A1-A4}, R^{B1-B4}, and R^{1-14} are such that they do not interfere with the cyclization process.

Where V represents a hydrogen atom, an oxidative intramolecular cyclization process, such as those described by Black *et al, Tetrahedron Lett.*, 1989, **30,** 5807 and Kita *et al, Chem. Commum,* 1996, 1481, may be used to effect the cyclization.

Alternatively, when V is a halogen atom, the intramolecular cyclization may proceed via the generation of a suitable radical in an analogous manner to those described by Antonio *et al, Can. J. Chem.*, 1994, **72**, 15 and Moody *et al, Tetrahedron Lett.*, 1995, **36**, 9501.

Yet another method for intramolecularly cyclizing a compound of Formula (I), when V is halogen, involves a Pd[0]-mediated cyclization. The intramolecular Pd[0]-catalyzed olefination of an organic halide (intramolecular Heck Reaction) is known to those skilled in the art and can be carried out by any suitable combination of reagents which will provide palladium in the zero state (Pd[0]).

Suitable combinations of reagents for effecting Pd[0]-catalysed cyclization are described, for example, in Burwood *et al, Tetrahedron Lett.*, 1995, **36**, 9053; Desarbe *et al, Heterocycles*, 1995, **41**, 1987; Harayoma *et al, Chem. Pharm. Bull.*, 1997, **45**, 1723; and Grigg *et al, Tetrahedron*, 1995, **50**, 359.

Thus, in one embodiment of the invention, Pd[0]-catalysed cyclization of Formula (I) may be effected by generating Pd[0] *in situ* by a combination of a Pd[II] reagent and a "ligand", and further providing a base for regeneration of the Pd[0] catalyst.

Suitable examples of a Pd[II]/Pd[0] reagent include, but are not limited to: $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$, $PdCl_2(PPh_3)_2$, $Pd(C_6H_5CN)_2Cl_2$, Pd(dibenzylideneacetone)$_3$.

Suitable examples of "ligand" providing reagents include, but are not limited to: PPh_3, P(o-tolyl)$_3$; 1,3-bis[diphenylphosphino]propane and 1,3-bis[diphenylphosphino]ethane.

Suitable bases for regenerating Pd[0] from Pd[II], which is formed during the Pd[0]-catalysed cyclization, include, but are not limited to; alkylamines, such as triethylamine and diisopropylethylamine; acetates, such as sodium acetate and potassium acetate; carbonates such as potassium carbonate, sodium carbonate, silver carbonate; and hydroxides such as sodium and potassium hydroxide.

When a compound of Formula (Ia) or (Ib) is treated to effect a double cyclization, to form compounds of Formula (Ia) or (IIb), the cyclizations may be effected by the radical, oxidative or Pd-mediated cyclization procedures as described above, and each cyclization may be effected in the same, similar or different manner.

Thus, in one embodiment, the two cyclizations may be performed sequentially, in any order, and may optionally employ different reagents and conditions, for example as described above. Optionally, after one cyclization, is performed, the mono-cyclized product may be isolated before being treated under suitable sonditions to perform the second intramolecular cyclization. In another form, the "double cyclization" may be effected in "one-pot", preferably under a single set of reaction conditions..

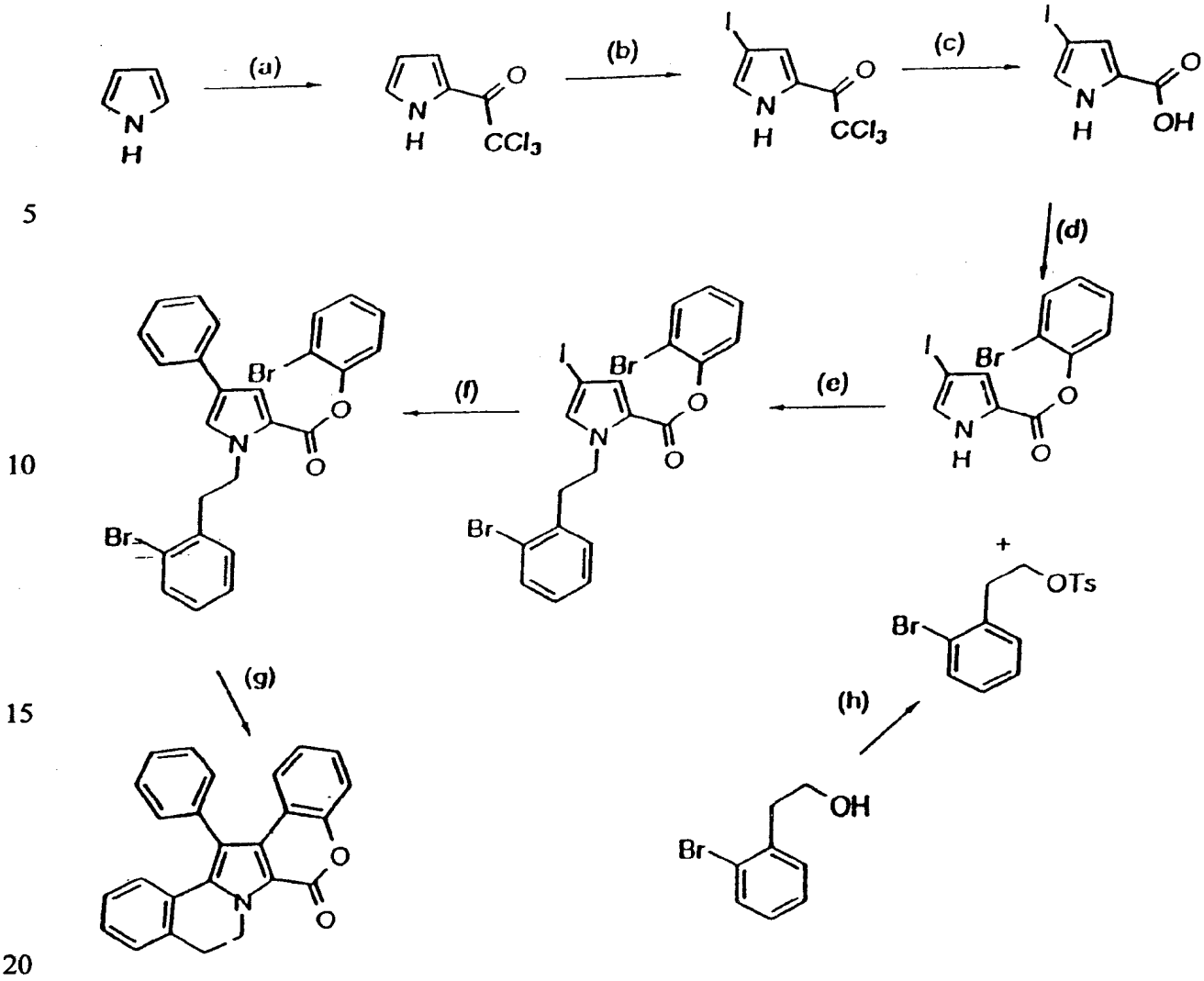
In a more preferred form, a compound of Formula (Ia), preferably (Ib), is made to undergo a "double cyclization" to form a compound of Formula (IIa), preferably (IIb), under Pd[0]-catalysed conditions.

In an even more preferred form, both cyclizations are effected in "one-pot" under a single set of reaction conditions.

The compounds of Formula (I), (Ia) and (Ib) may be prepared, starting from a pyrrole core, by standard procedures known to the skilled addressee for effecting substitution of the carbon atoms of the pyrrole core, for example by electrophilic aromatic substitution or halogenating the pyrrole nucleus and effecting a substitution by Stille, Suzuki, or Negishi cross-coupling reactions with stannane, boronic acid or zinc compounds such as aryl-stannanes, aryl boronic acid and aryl zinc compounds. Substitution of the N-atom can be effected by standard procedures.

One suitable approach, although by no means limiting, is depicted below in Scheme 1 which is considered to be illustrative of suitable methods for substituting the pyrrole nucleus.

It will be understood that by use of the appropriate reagents in steps used to introduce the 1-, 2-, 4- substitution pattern of the pyrrole core, for example, the phenyl containing reagents used in steps, (d), (e) and (f) wherein the phenyl moiety is further substituted as hereinbefore described, a range of substitution patterns and substituents may be introduced to form the intermediates amenable to the cyclization processes and the formation of the corresponding cyclized compounds.



Scheme 1

Scheme 1: *Reagents and conditions:* (a) Cl_3CCOCl (1 mole equiv.), Et_2O, 35°C, 1h (80%); (b) I_2 (1 mole equiv.), AgO_2CCF_3 (1 mole equiv.), $CHCl_3$, 18°C, 1h (82%); (c) K_2CO_3 (2M in H_2O), DMSO, 18°C, 32 h (92%); (d) (i) $(COCl)_2$ (1.1 mole equiv.), DMF (cat.), CH_2Cl_2, 18°C, 2 h; (ii) o-bromophenol (1 mole equiv.), DMAP (cat.), CH_2Cl_2, 18°C, 1 h (92%); (e) K_2CO_3 (1.14 mole equiv.), Bu_4NCl (0.1 mole equiv.), DMF, 80°C, 2 h (90%): (f) PhZnCl (1.3 mole equiv.), $PdCl_2(PPh_3)_2$ (0.05 mole equiv.), THF/DMF, 18°C, 1 h (95%); (g) $Pd(OAc)_2$ (0.5 mole equiv.), PPh_3 (1 equiv.), NaOAc (4 equiv.), DMF, 130°C, 6 h (16%); (h) TsCl (2.4 mole equiv.), KOH (2.4 mole equiv.), Et_2O, 0 ®18°C, 2 h (98%).

Where the optional double bond is present, as in the compounds of Formula (II) which contain moiety of Formula (I), such as compounds of Formula (IIb), this may be introduced either by dehydrogenation of the cyclized product, or alternatively, by incorporation of the corresponding double bond into a precursor thereof. Suitable methods therefor will be known to the skilled addressee (see for example, *Advanced Organic Chemistry, Reactions, Mechanisms , and Structure* by Jerry March, Third Edition, Wiley Interscience). One such suitable method comprises treating the cyclized compound of Formula (IIb), with DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoqionone). For example, Lamellarin T diisopropylether (Compound 37 in Table 2) can be converted into Lamellarin W diisopropylether (Compound 11 in Table 1) by treatment with DDQ in dry chloroform at 60-65C (see Example 11 in WO98/50365)

WO 97/01336 (the entire contents of which are taken to be incorporated herein by reference) describes Lamellarin class compounds as having inhibitory and/or cytotoxic activity against multidrug resistant-type tumours.

Accordingly, yet another aspect of the present invention contemplates a method of treatment comprising the administration of a treatment effective amount of a compound of general Formula (II), as prepared by the methods described herein, as an active ingredient, to an animal, including a human, in need thereof.

As used herein, the term "effective amount" relates to an amount of compound which, when administered according to a desired dosing regimen, provides the desired therapeutic activity. The dose will depend on the age, weight and condition of the subject and it is within the skill of the attending physician to determine suitable doasages. Dosing may occur at intervals of minutes, hours, days, weeks, months or years or continuously over any one of these periods. Suitable dosages lie within the range of about 0.1 ng per kg of body weight to 1 g per kg of body weight per dosage. Preferably, the dosage is in the range of 1 μg to 1 g per kg of body weight per dosage. More preferably, the dosage is in the range of 1 mg to 1 g per dosage per kg of body weight. Suitably, dosages are in the range of about I mg to 500 mg per kg of body weight, such as between 1 mg and 250 mg

or 1 mg and 100 mg .

In a preferred embodiment, the method of treatment relates to treating multidrug resistant tumors.

In another embodiment, the method of treatment contemplates improving the antitumor chemotherapeutic effect of multidrug resistant affected drugs.

In another preferred embodiment, the method of treatment is a method for inducing apoptosis. More preferably, the method of treatment is a method of inducing apoptosis on a multidrug resistant cell

In another embodiment, the method of treatment contemplates modulating immunological functions.

The active ingredient may be administered in a single dose or a series of doses. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a composition, preferably as a pharmaceutical composition.

Yet another aspect of the invention contemplates compositions comprising a compound of general Formula (II), as prepared according to the present invention, together with a pharmaceutically acceptable carrier, excipient or diluent.

The carrier must be pharmaceutically "acceptable" in the sense of being compatible with the other ingredients of the composition and not injurious to the subject. Compositions include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parental (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared

by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g inert diluent, preservative disintegrant (e.g. sodium starch glycolate, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured base, usually sucrose and acacia or tragacanth gum; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia gum; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Compositions for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Compositions suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bactericides and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage compositions are those containing a daily dose or unit, daily sub-dose, as herein above described, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the active ingredients particularly mentioned above, the compositions of this invention may include other agents conventional in the art having regard to the type of composition in question, for example, those suitable for oral administration may include such further agents as binders, sweeteners, thickeners, flavouring agents disintegrating agents, coating agents, preservatives, lubricants and/or time delay agents. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, xanthan gum, bentonite, alginic acid or agar. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl

paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

The present invention also provides the use of a compound of general Formula (II), as prepared according to the present invention, in the manufacture of a medicament for treatment of an animal or human in need thereof.

Another aspect of the invention contemplates an agent for the treatment of an animal or human in need thereof comprising a compound of general Formula (II), as prepared according to the present invention.

In a first embodiment, the agent is for treating multidrug resistant tumors.

In another embodiment the agent is for inducing apoptosis on a multi-drug resistant cell.

In yet another embodiment, the agent is for improving the anti-tumour chemotherapeutic effect of multidrug resistant affected drugs.

A further embodiment is an agent for modulating immunological functions.

Suitable, although by no means limited, examples of compounds which may be prepared via the intermediates of the present invention are depicted below in Tables 1 and 2:

Table 1

Compound	R^1	R^2	R^3	R^4 R_5	R^6	R^7	R^8 $R9$	R^{10}	R^{11}	R^{12} R^{13}
1	H	H	H	H	H	H	H	H	H	H
2(Lamellarin B)	OMe	OMe	OMe	H	OMe	OH	H	OMe	OH	H
3(Lamellarin D)	H	OH	OMe	H	OMe	OH	H	OMe	OH	H
4(Lamellarin D-triacetate)	H	OAc	OMe	H	OMe	OAc	H	OMe	OAc	H
5(Lamellarin M)	OH	OMe	OMe	H	OMe	OH	H	OMe	OH	H
6(Lamellarin M-triacetate)	OAc	OMe	OMe	H	OMe	OAc	H	OMe	OAc	H

Compound	R^1	R^2	R^3	R4 R5	R^6	R^7	R^8 R9	R^{10}	R^{11}	R^{12} R^{13}
7(Lamellarin N)	H	OH	OMe	H	OMe	OH	H	OH	OMe	H
8(Lamellarin N-triacetate)	H	OAc	OMe	H	OMe	OAc	H	OAc	OMe	H
9(Lamellarin W)	OMe	OMe	OMe	H	OMe	OH	H	OH	OMe	H
10(Lamellarin X)	OH	OMe	OMe	H	OMe	OH	H	OH	OMe	H
11	OMe	OMe	OMe	H	OMe	O^{i}Pr	H	O^{i}Pr	OMe	H

Table 2.

Compound	R^1	R^2	R^3	R^4 $R5$	R^6	R^7	R^8 R^9	R^{10}	R^{11}	R^{12} R^{13}	R^{14}
12 (Lamellarin A)	OMe	OMe	OMe	H	OMe	OH	H	OMe	OH	H	OH
13 (Lamellarin C)	OMe	OMe	OMe	H	OMe	OH	H	OMe	OH	H	H
14 (Lamellarin E)	OH	OMe	OMe	H	OMe	OH	H	OH	OMe	H	H
15(Lamellarin F)	OH	OMe	OMe	H	OMe	OH	H	OMe	OMe	H	H
16 (Lamellarin G)	H	OH	OMe	H	OH	OMe	H	OH	OMe	H	H
17 (Lamellarin H)	H	OH	OH	H	OH	OH	H	OH	OH	H	H

Compound	R^1	R^2	R^3	R^4 R_5	R^6	R^7	R^8 R^9	R^{10}	R^{11}	R^{12} R^{13}	R^{14}
18 (Lamellarin I)	OMe	OMe	OMe	H	OMe	OH	H	OMe	OMe	H	H
19 (Lamellarin I-acetate)	OMe	OMe	OMe	H	OMe	OAc	H	OMe	OMe	H	H
20 (Lamellarin J)	H	OH	OMe	H	OMe	OH	H	OMe	OMe	H	H
21 (Lamellarin K)	OH	OMe	OMe	H	OMe	OH	H	OMe	OH	H	H
22 (Lamellarin K-triacetate)	OAc	OMe	OMe	H	OMe	OAc	H	OMe	OAc	H	H
23 (Lamellarin L)	H	OH	OMe	H	OMe	OH	H	OH	OMe	H	H
24 (Lamellarin L-triacetate)	H	OAc	OMe	H	OMe	OAc	H	OAc	OMe	H	H
25 (Lamellarin S)	H	OH	OMe	H	OH	OH	H	OH	OH	H	H
26 (Lamellarin T)	OMe	OMe	OMe	H	OMe	OH	H	OH	OMe	H	H

Compound	R^1	R^2	R^3	R^4 R_5	R^6	R^7	R^8 R^9	R^{10}	R^{11}	R^{12} R^{13}	R^{14}
27 (Lamellarin T20-sulfate)	OMe	OMe	OMe	H	OMe	OSO_3 Na	H	OMe	OH	H	H
28	H	OMe	OMe	H	H	H	H	H	H	H	H
29 (Lamellarin U)	H	OMe	OMe	H	OMe	OH	H	OH	OMe	H	H
30 (Lamellarin U20-sulfate)	H	OMe	OMe	H	OMe	OSO_3 Na	H	OH	OMe	H	H
31 (Lamellarin V)	OMe	OMe	OMe	H	OMe	OH	H	OH	OMe	H	OH
32 (Lamellarin V20-sulfate)	OMe	OMe	OMe	H	OMe	OSO_3 Na	H	OH	OMe	H	OH
33 (Lamellarin Y20-sulfate)	H	OMe	OH	H	OMe	OSO_3 Na	H	OH	OMe	H	H
34	H	OMe	OMe	H	OMe	O^iPr	H	OMe	O^iPr	H	H
35	H	OMe	OMe	H	OMe	OH	H	OMe	OH	H	H

Compound	R^1	R^2	R^3	R^4 R_5	R^6	R^7	R^8 R^9	R^{10}	R^{11}	R^{12} R^{13}	R^{14}
36	O^{i}Pr	OMe	OMe	H	OMe	O^{i}Pr	H	OMe	O^{i}Pr	H	H
37	OMe	OMe	OMe	H	OMe	O^{i}Pr	H	O^{i}Pr	OMe	H	H
38	H	OMe	OMe	H	OMe	O^{i}Pr	H	O^{i}Pr	OMe	H	H
39 (Lamellarin T diacetate)	OMe	OMe	OMe	H	OMe	OAc	H	OAc	OMe	H	H

The invention will now be described with reference to the following Examples. However, it is to be understood that these do not supercede the generality of the preceding description.

EXAMPLES

Example 1

2-(Trichloroacetyl)pyrrole

2-(Trichloroacetyl)pyrrole was prepared from pyrrole (12.5 g, 186 mmol) and trichloroacetyl chloride (36.5 g, 200 mmol) according to the method of Bailey *et al*, *Org.Synth.*, **1971**, 100. In this manner the title compound (31.3 g, 80%) was obtained as a cream solid, m.p. 73-74 °C (lit. m.p. 73-75 °C). ^{1}H n.m.r. d 9.30, broad s, 1H; 7.39, m, 1H; 7.17, m, 1H; 6.40, dt, *J* 3.9 and 2.4 Hz, 1H. (see also *J. Org. Chem.*, **1972**, *37*, 3618; **1993**, *58*, 7245).

4-Iodo-2-(trichloroacetyl)pyrrole

The title compound was prepared from 2-(trichloroacetyl)pyrrole according to the method of Bélanger, *Tetrahedron Lett.*, **1979**, 2505. Thus, iodine (12.0 g, 47.2 mmol) was added portionwise (approximately 1 g per portion) over 0.17 h to a magnetically stirred mixture of silver trifluoroacetate (11.0 g, 49.8 mmol) and 2-(trichloroacetyl)pyrrole (10.0 g, 47.1 mmol) in dry chloroform (70 ml) maintained at 0 °C (ice-bath). After addition was complete the reaction mixture was allowed to warm to 18 °C and stirred at this temperature for a further 2 h. The resultant suspension was filtered through a sintered glass funnel (No. 3 porosity) and the filtrate washed with $Na_2S_2O_5$ (1 x 80 ml of 5% w/v aqueous solution) and water (2 x 80 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The solid residue thus obtained was treated with hexane/ether (50 ml of a 4:1 v/v mixture) and the resulting suspension stirred at 18 °C for 5 h then the solid was filtered off to give the title compound (13.1 g, 82%) as a cream solid, m.p. 129-130 °C (lit. m.p. 128-130 °C). ^{1}H n.m.r. d 9.45, broad s, 1H; 7.44, dd, *J* 2.6 and 1.3 Hz, 1H; 7.19, dd, *J* 2.6 and 1.3 Hz, 1H.

4-Iodopyrrole-2-carboxylic acid

K_2CO_3 (100 ml of a 2 M aqueous solution) was added to a solution of 4-iodo-2-(trichloroacetyl)pyrrole (8.5 g, 2.5 mmol) in dmso (30 ml) and the resulting mixture stirred at 18 °C for 3 h then diluted with H_2O (200 ml). The solution thus obtained was washed with ethyl acetate (2 x 100 ml) then acidified, by dropwise addition of HCl (2 M aqueous solution), to pH 3. The resulting slurry was extracted with ethyl acetate (3 x 100 ml) and the combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *title compound (8)* (5.51 g, 92%) as a white solid, m.p. 200 °C (Found: $M^{+\cdot}$, 236.9285. $C_5H_4INO_2$ requires $M^{+\cdot}$, 236.9287). n_{max} (KBr) 3287, 3129, 3035, 1703, 1544, 1430, 1300, 1212, 1122 cm^{-1}. ^1H n.m.r. [300 MHz, 3:1 $(CD_3)_2SO/CDCl_3$] d 11.98, broad s, 1H; 6.98, t, *J* 1.5 Hz, 1H; 6.76, broadened s, 1H (resonance due to N-H not observed). ^{13}C n.m.r. [75.5 MHz, 3:1 $(CD_3)_2SO/CDCl_3$] d 159.0 (C), 126.0 (CH), 123.3 (C), 118.8 (CH), 59.0 (C). Mass spectrum *m/z* 237 (100%) ($M^{+\cdot}$); 219 (87) [$(M - H_2O)^{+\cdot}$].

2-Bromophenyl 4-Iodopyrrole-2-carboxylate

Oxalyl chloride (203 mL, 2.32 mmol) was added to a magnetically stirred suspension of 4-iodopyrrole-2-carboxylic acid (8) (500 mg, 2.11 mmol) in dry CH_2Cl_2 (15.0 ml) containing dmf (1 drop). After stirring the resulting solution at 18 °C for 2 h it was added to a magnetically stirred solution of *o*-bromophenol (363 mg, 2.11 mmol), triethylamine (660 ml, 4.73 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (dmap, several crystals) in CH_2Cl_2 (10 ml). After 1 h the reaction mixture was concentrated onto silica gel (5 g) and the residue subjected to flash chromatography (silica gel, 3:1 hexane/ether elution). Concentration of the appropriate fractions (R_f 0.2) then gave the *title compound* (761 mg, 92%) as a white crystalline solid, m.p. 126-127 °C (Found: C, 33.9; H, 1.7; Br, 20.4; I, 32.4; N, 4.0. $C_{11}H_7BrINO_2$ requires C, 33.7; H, 1.8; Br, 20.4; I, 32.4; N, 3.6%). n_{max} (KBr) 3383, 2969, 1709, 1580, 1541, 1472, 1444, 1377, 1312, 1218, 1169, 1133, 1043 cm^{-1}. ^1H n.m.r. d 9.57, broad s, 1H; 7.65, dd, *J* 8.1 and 1.5 Hz, 1H; 7.37, td, *J* 8.1 and 1.5 Hz, 1H; 7.27, m, 2H; 7.18, td, *J* 8.1 and 1.5 Hz, 1H; 7.08, m, 1H. ^{13}C n.m.r. d 158.0 (C), 148.3 (C), 134.0 (CH), 129.8 (CH), 129.1 (CH), 128.1 (CH), 124.4 (CH), 124.3 (CH), 123.6 (C), 116.9 (C), 62.9 (C). Mass spectrum *m/z* 393 (24%) 391 (22) ($M^{+\cdot}$); 220 (100) [$(M - C_6H_4BrO)^{+\cdot}$].

2-(2-Bromophenyl)ethyl 4-Methylbenzenesulfonate (13)

A magnetically stirred solution of 2-bromophenethyl alcohol (5.00 g, 24.9 mmol, ex ALDRICH) and 4-methylbenzenesulfonyl chloride (11.20 g, 59.7 mmol) in diethyl ether (50 ml) was cooled to 0 °C (ice-bath) then treated with powdered KOH (3.2 g, 2.4 mole equiv.). The reaction mixture thus obtained was allowed to warm to 18 °C, stirred at this temperature for 2.0 h then diluted with water (100 ml). The separated organic phase was washed with water (1 x 100 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a white solid. Since this material contained residual 4-methylbenzenesulfonyl chloride it was dissolved in pyridine (75 ml) and the resulting solution stirred at 18 °C for 0.16 h then diluted with water (500 ml) and extracted with diethyl ether (1 x 500 ml). The separated organic phase was washed with HCl (1 x 250 ml of a 5 M aqueous solution) then sodium hydrogen carbonate (1 x 250 ml of a 0.5 M aqueous solution) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the title compound (8.66 g, 98%) as white crystalline masses, m.p. 39-39.5 °C (Found: C, 50.9; H, 4.2; Br, 22.6; S, 8.8. $C_{15}H_{15}BrO_3S$ requires C, 50.7; H, 4.3; Br, 22.5; S, 9.0%). n_{max} (KBr) 1356, 1177, 1021, 980, 962, 895, 812, 769, 752, 665, 557 cm^{-1}. ^1H n.m.r. d 7.68, d, *J* 8.3 Hz, 2H; 7.45, d, *J* 7.7 Hz, 1H; 7.27, d, *J* 8.3 Hz, 2H; 7.17, m, 2H; 7.07, m, 1H; 4.25, t, *J* 7.0 Hz, 2H; 3.09, t, *J* 7.0 Hz, 2H; 2.43, s, 3H. ^{13}C n.m.r. d 144.5 (C), 135.3 (C), 132.7 (CH), 132.8 (C), 131.3 (CH), 129.7 (CH), 128.5 (CH), 127.6 (CH), 127.4 (CH), 124.2 (C), 68.6 (CH_2), 35.5 (CH_2), 21.5 (CH_3). Mass spectrum *m/z* 356 (0.7%) 354 (0.7) ($M^{+\cdot}$); 184 (98) 182 (100) [M -$H_3CC_6H_4SO_3H)^{+\cdot}$]; 171 (49) 169 (51); 155 (45); 103 (32); 91 (80) (C_7H_7+).

2-Bromophenyl 1-[2'-(2"-Bromophenyl)ethyl]-4-iodopyrrole-2-carboxylate

Compound (13) (700 mg, 1.97 mmol), tetraethyl ammonium chloride (30 mg, 0.18 mmol) and K_2CO_3 (278 mg, 2.0 mmol) were added to a solution of compound (11) (700 mg, 1.79 mmol) in dry dmf (30 ml) and the resultant slurry stirred at 80 °C for 2 h. The cooled reaction mixture was diluted with ethyl acetate (150 ml) and washed with water (3 x 150 ml). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced

pressure. The solid residue thus obtained was subjected to flash chromatography (silica gel, 4:1 hexane/ether elution) and concentration of the appropriate fractions (R_f 0.5, 3:1 hexane/ether elution) gave the *title compound (14)* (920 mg, 89%) as a white crystalline solid, m.p. 122-123 °C (Found: C, 39.5; H, 2.1; Br, 27.6; I, 22.1; N, 2.3. $C_{19}H_{14}Br_2INO_2$ requires C, 39.7; H, 2.5; Br, 27.8; I, 22.1; N, 2.4%). n_{max} (KBr) 2949, 1716, 1517, 1468, 1438, 1411, 1374, 1326, 1232, 1216, 1191, 1055, 1028 cm^{-1}. ^1H n.m.r. d 7.65, dd, *J* 7.8 and 1.8 Hz, 1H; 7.55, dd, *J* 7.8 and 1.8 Hz, 1H; 7.37, m, 2H; 7.28-7.04, m, 5H; 6.70, d, *J* 2.1 Hz, 1H; 4.55, t, *J* 7.5 Hz, 2H; 3.20, t, *J* 7.5 Hz, 2H. ^{13}C n.m.r. d 157.0 (C), 147.8 (C), 136.9 (C), 134.5 (CH), 133.3 (CH), 132.7 (CH), 131.2 (CH), 128.6 (CH), 128.4 (CH), 127.6 (CH), 127.3 (CH), 126.7 (CH), 124.4 (C), 124.0 (CH), 122.0 (C), 116.6 (C), 59.6 (C), 49.0 (CH_2), 38.0 (CH_2). Mass spectrum *m/z* 577 (1%) 575 (2) 573 (1) ($M^{+\cdot}$); 496 (10) 494 (11) [$(M - Br^{\cdot})^+$]; 404 (98) 402 (100) [$(M - C_6H_4BrO^{\cdot})^+$].

2-Bromophenyl 1-[2'-(2"-Bromophenyl)ethyl]-4-phenylpyrrole-2-carboxylate (4)

Phenylzinc chloride [prepared by the addition of anhydrous zinc chloride (540 mg, 3.96 mmol) to a solution of phenyllithium (2.0 ml of a 1.8 M solution in cyclohexane/ether, 3.6 mmol) in thf (4.0 ml)] was added dropwise, over 2 min., to a magnetically stirred solution of compound (14) (1.75 g, 3.04 mmol) and $Pd(PPh_3)_2Cl_2$ (106 mg, 0.152 mmol) in dmf (15 ml). Stirring was continued at 18 °C for 1 h then the reaction mixture was transferred to a separatory funnel, diluted with ethyl acetate (100 ml) and washed with NH_4Cl (100 ml of a saturated aqueous solution) then H_2O (2 x 100 ml). The separated organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give light-yellow oil which was subjected to flash chromatography (silica, 2:1 hexane/CH_2Cl_2 elution). Concentration of the appropriate fractions (R_f 0.5) gave the *title compound* (1.52 g, 95%) as a microcrystalline solid, m.p. 90-92 °C (Found: C, 57.1; H, 3.4; Br, 30.7; N, 2.5. $C_{25}H_{19}Br_2NO_2$ requires C, 57.2; H, 3.7; Br, 30.4; N, 2.7%). n_{max} (KBr) 2958, 2930, 1718, 1603, 1580, 1562, 1472, 1397, 1215, 1196, 1066, 1024 cm^{-1}. ^1H n.m.r. d 7.70, dd, *J* 8.0 and 1.5 Hz, 1H; 7.60-7.00, m, 14H; 4.63, t, *J* 6.9 Hz, 2H; 3.32, t, *J* 6.9 Hz, 2H. ^{13}C n.m.r. (75.5 MHz, $CDCl_3$) d 158.4 (C), 148.3 (C), 137.5 (C), 134.2 (C), 133.5 (CH), 132.9 (C), 131.5 (CH), 128.9 (CH), 128.6(3) (CH), 128.6(1) (CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 126.5 (CH), 125.4 (CH), 124.8 (C), 124.6 (C),

124.4 (CH), 120.9 (C), 117.5 (CH), 116.9 (C), 49.3 (CH_2), 38.2 (CH_2). Mass spectrum *m/z* 527 (3%) 525 (6) 523 (3) ($M^{+\cdot}$); 446 (12) 444 (11) [(M -Br$^{\cdot}$]; 354 (100) 352 (96) [(M - $C_6H_4BrO^{\cdot})^+$].

14-Phenyl-8,9-dihydro-6H-[1]benzopyrano[4',3':4,5]pyrrolo[2,1-a]isoqinolin-6-one

$Pd(OAc)_2$ (32 mg, 0.143 mmol) was added to a magnetically stirred solution of compound (4) (148 mg, 0.282 mmol), NaOAc (92.7 mg, 1.13 mmol) and PPh_3 (74.0 mg, 0.282 mmol) in dmf (2 ml) contained in a Schlenk tube. The resulting mixture was evacuated (1.0 mmHg) and back-filled with N_2 (gas) three times (to remove dissolved oxygen) then heated under nitrogen at 135 °C for 6 h. The cooled reaction mixture was diluted with ether (25 mL) and washed with brine (2 x 20 ml) then water (20 ml) before being dried ($MgSO_4$), filtered and concentrated onto silica (2 g). The residue was subjected to flash chromatography (silica, 1:2, 1:1 then 2:1 CH_2Cl_2/hexane elution) and the appropriate fractions (R_f 0.3, 2:1 CH_2Cl_2/hexane elution) were concentrated under reduced pressure to give the *title compound* (16 mg, 16%) as a cream-coloured microcrystals, m.p. 259-260 °C (Found: $M^{+\cdot}$, 363.1257. $C_{25}H_{17}NO_2$ requires $M^{+\cdot}$, 363.1259). n_{max} (KBr) 2925, 2853, 1708, 1449, 1420, 1396, 1339, 1281, 1241, 1198, 1151, 1133, 1106, 1085, 1047 cm^{-1}. ^1H n.m.r. d 7.58-7.55, m, 2H; 7.51-7.50, m, 2H; 7.40, dd, *J* 7.5 and 0.9 Hz, 1H; 7.32-7.18, m, 4H; 7.10, dd, *J* 7.8 and 1.2 Hz, 1H; 7.01-6.97, m, 3H; 4.88, t, *J* 6.9 Hz, 2H; 3.21, t, *J* 6.9 Hz, 2H. ^{13}C n.m.r. d 155.3 (C), 151.2 (C), 135.6 (C), 135.3 (C), 133.8 (C), 130.7 (CH), 129.4 (CH), 128.3 (CH), 128.1 (CH), 127.5 (C), 127.4 (CH), 126.9 (CH), 125.7 (CH), 123.7 (CH), 123.3 (CH), 118.2 (C), 117.5 (C), 117.1 (CH), 42.3 (CH_2), 29.3 (CH_2) (three peaks obscured or overlapping). Mass spectrum *m/z* 363 (100%) ($M^{+\cdot}$).

2'-Bromophenyl 5,6-Dihydro-1-phenylpyrrolo[2,1-a]isoquinoline-3-carboxylate (16) and Bromo{2'-(5",6"-dihydro-1"-phenylpyrrolo[2",1"-a]isoquinoline-3"-carboxy)phenyl}bis -(triphenylphosphine)palladium (17)

$Pd(OAc)_2$ (197 mg, 0.88 mmol) was added to a solution of compound (4) (230 mg, 0.438 mmol), NaOAc (80 mg, 0.975 mmol) and PPh_3 (460 mg, 1.75 mmol) in dmf (20 ml). The

solution was evacuated (1.0 mmHg) and back-filled with N_2 (gas) three times to remove dissolved oxygen and then heated under nitrogen at 110 °C for 19 h. The cooled reaction mixture was diluted with ethyl acetate (25 ml) then washed with brine (2 x 20 ml) and water (1 x 20 ml). The separated organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure onto silica (2 g). Subjection of the resulting material to flash chromatography (silica, 1:2 then 1:1 CH_2Cl_2/hexane followed by 4:1 CH_2Cl_2/ethyl acetate elution) gave two fractions, A and B.

Concentration of fraction A (R_f 0.6, 2:1 CH_2Cl_2/hexane elution) afforded compound (16) (34 mg, 17%) as off-white crystalline masses, m.p. 130-131 °C (Found: $M^{+\cdot}$, 443.0529. $C_{25}H_{18}79BrNO_2$ requires $M^{+\cdot}$, 443.0521). n_{max} (KBr) 2950, 1710, 1471, 1439, 1418, 1240, 1212, 1176, 1046 cm^{-1}. ^1H n.m.r. d 7.57, dd, *J* 8.1 and 1.5 Hz, 1H; 7.45-7.05, m, 12H; 6.95, br t, *J* 8.1 Hz, 1H; 4.57, t, *J* 6.3 Hz, 2H; 3.05, t, *J* 6.3 Hz, 2H. ^{13}C n.m.r. d 158.5 (C), 148.1 (C), 136.1 (C), 133.4 (C), 133.3 (CH), 132.9 (C), 129.1 (CH), 128.6 (C), 128.4 (CH), 128.1 (C), 127.9 (CH), 127.7 (CH), 127.1 (CH), 126.9 (CH), 126.7 (CH), 125.5 (CH), 124.2 (CH), 123.5 (C), 121.3 (CH), 119.4 (C), 116.7 (C), 42.4 (CH_2), 29.5 (CH_2). Mass spectrum *m/z* 445 (10%) 443 (9) ($M^{+\cdot}$); 272 (100) [$(M - C_6H_4BrO\cdot)^+$].

Concentration of fraction B (R_f 0.1, CH_2Cl_2 elution) afforded compound (17) (40 mg, 8.5%) as off-white crystalline masses, m. p. 159-162 °C. n_{max} (KBr) 3052, 2923, 1705, 1481, 1435, 1416, 1238, 1172, 1095, 1058, 1024 cm^{-1}. ^1H n.m.r. d 7.65-7.40, m, 18H; 7.30-7.05, m, 22H; 6.58, m, 1H; 6.52, t, *J* 6.6 Hz, 1H; 6.39, m, 1H; 6.07, q, *J* 6.6 Hz, 1H; 4.73, m, 2H; 3.05, m, 2H. ^{13}C n.m.r. d 159.2 (C), 151.8 (C), 138.3 (CH), 136.5 (C), 134.8 (CH), 133.2 (C), 131.8 (C), 131.5 (C), 131.0 (C), 129.9 (CH), 129.8 (CH), 129.5 (CH), 129.0 (CH), 128.7 (C), 127.8 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 125.7 (CH), 125.0 (CH), 123.2 (C), 123.0 (CH), 121.9 (CH), 121.1 (C), 120.5 (CH), 42.2 (CH_2), 29.7 (CH_2). Mass spectrum *m/z* 365 (6) [$(M - Pd(PPh_3)_2Br + H)^{+\cdot}$]; 277 (26); 272 (32) {[$M - C_6H_4OPd(PPh_3)_2Br$] }; 262 (100) ($Ph_3P^{+\cdot}$).

1-Phenylpyrrolo[2,1-a]isoquinoline (18) and 1-[2'-(2"-Bromophenyl)ethyl]-4-phenylpyrrole (19)

A solution of the dibromide (4) (13 mg, 25 mmol), *trans*-di(m-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) *Chem., Eur., J.*, 1997, 3, 1357, (2.5 mg, 2.5 mmol) and

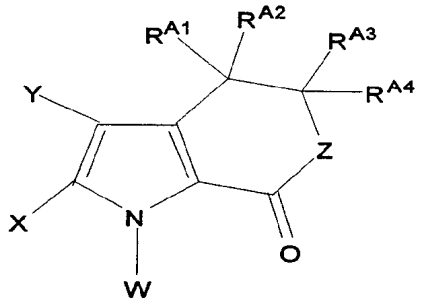
anhydrous sodium acetate (6.2 mg, 75 mmol) in degassed *N,N*-dimethylacetamide (0.25 ml) was heated, under nitrogen, at 140 °C for 72 h. The cooled reaction mixture was then diluted with diethyl ether (5 ml) and the resulting solution washed with brine/water (3 x 5 ml of a 1:1 v/v mixture). The organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 3:7 then 7:3 CH_2Cl_2/hexane elution) gave, after concentration of the appropriate fractions (R_f 0.7, 3:7 CH_2Cl_2/hexane elution), a 1:3 mixture of compounds (18) and (19) (4 mg, 52% combined yield) as a light-yellow and unstable oil. n_{max} (KBr) 1705, 41.2, 1555, 1500, 1471, 1441, 1359, 1202, 1071, 1027, 751, 694, 655 cm^{-1}. ^1H n.m.r. d [compound (18)] 7.60-6.95, complex m, 9H; 6.92, t, *J* 2.0 Hz, 1H, H-2; 6.63, t, *J* 1.6 Hz, 1H, H-5; 6.43, broadened t, *J* 2.3 Hz, 1H, H-4; 4.14, t, *J* 7.7 Hz, 2H; 3.22, t, *J* 7.7 Hz, 2H; [compound (19)] 7.60-6.95, complex m, 9H; 6.73, d, *J* 2.7 Hz, 1H, H-3; 6.23, d, *J* 2.7 Hz, 1H, H-2; 4.08, t, *J* 7.7 Hz, 2H; 3.10, t, *J* 7.7 Hz, 2H. G.c./m.s. [compound (18)] (R_t 4.52 min.) 245 (100) ($M^{+\cdot}$), 167 (21), 149 (28), 120 (6); [compound (19)] (R_t 5.85 min.) 327 (12) 325 (12) ($M^{+\cdot}$), 246 (100) $[(M - Br^{\cdot})^+]$.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

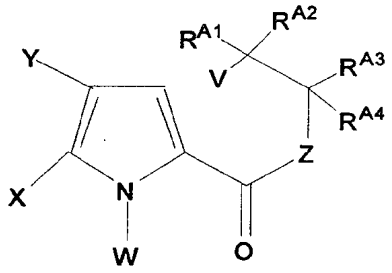
CLAIMS;

1. A method for the preparation of a compound of Formula (II).



(II)

comprising the step of performing an intramolecular cyclization of a compound of Formula (I):



(I)

wherein:

R^{A1-A4} are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano; or

R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic group; or

R^{A2} and R^{A3}, together with the carbon atoms to which they are attached form an optionally substituted saturated or unsaturated carbocyclic or heterocyclic group; or

$R^{A1}R^{A2}C\text{-}CR^{A3}R^{A4}$ forms an optionally substituted aryl group or aromatic heterocyclic group;

Y is selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano;

W and X are as defined for Y, or together with the nitrogen and carbon atoms to which they are attached, form a saturated or unsaturated nitrogen containing heterocyclic group which may be optionally substituted or optionally fused to a saturated or unsaturated carbocyclic group, aryl group or heterocyclic group;

V represents a halogen or hydrogen atom;

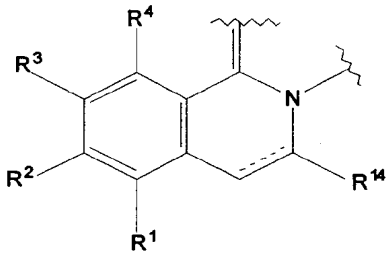
Z is $-(CH_2)_n-U-(CH_2)_o-$ where U is selected from CH_2, NH or a heteroatom, and n and o are independently selected from 0, 1, 2 or 3.

2. A method according to claim 1 wherein W and X together with the nitrogen and carbon atoms to which they are attached, form a saturated or unsaturated nitrogen containing heterocyclic group which may be optionally substituted or optionally fused to a saturated or unsaturated carbocyclic group, aryl group or heterocyclic group.

3. A method according to claim 2 wherein W and X, together with the nitrogen and carbon atoms to which they are attached, form a group selected from an optionally substituted quinolinyl group, optionally substituted isoquinolinyl group, optionally substituted dihydroquinolinyl group, optionally substituted dihydroisoquinolinyl group, optionally substituted pyridyl group or dihydro or tetrahydro congeners thereof, or optionally substituted phenanthridine.

4. A method according to claim 3 wherein W and X together with the nitrogen and

carbon atoms to which they are attached, form an optionally substituted isoquinolinyl or optionally substituted dihydroisoquinolinyl group of general Formula (i):

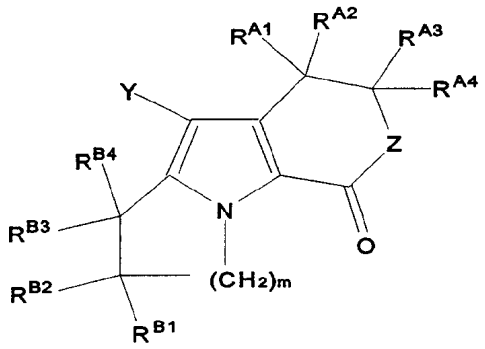


(i)

wherein R^1 - R^4 and R^{14} are as defined for Y in claim 1, and ----- represents an optional double bond.

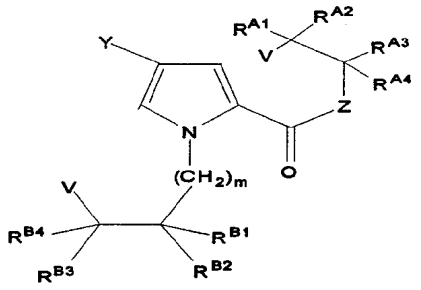
5. A method according to claim 4 wherein R^1 - R^4 are independently selected from the group consisting of hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester; optionally substituted amino; carboxamido; or sulfate; and R^{14} is hydrogen or hydroxy.

6. A method for the preparation of a compound of Formula (IIa):



(IIa)

comprising the step of performing two intramolecular cyclizations on a compound of Formula (Ia):



(Ia)

wherein:

R^{A1-A4} ,V, Y, Z are as defined in claim 1;

R^{B1-B4} are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano; or

R^{B2} and R^{B3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic group; or

R^{B2} and R^{B3}, together with the carbon atoms to which they are attached form an optionally substituted saturated or unsaturated carbocyclic or heterocyclic group; or

$R^{B1}R^{B2}C\text{-}CR^{B3}R^{B4}$ form an optionally substituted aryl group or aromatic heterocyclic group; and

m is selected from 1, 2, 3 or 4.

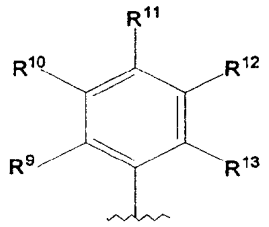
7. A method according to claim 6 wherein m is 1 or 2, preferably 2.

8. A method acccording to claim 1 or claim 6 wherein $R^{A1}R^{A2}C\text{-}CR^{A3}R^{A4}$ forms an aryl group or an aromatic heterocyclic group, said group selected from: an optionally substituted benzene or naphthalene ring or an optionally substituted pyridine, optionally substituted furan, optionally substituted pyrrole or optionally substituted thiophene and benzene-fused analogues thereof.

9. A method according to claim 8 wherein $R^{A1}R^{A2}C\text{-}CR^{A3}R^{A4}$ forms an optionally substituted benzene group.

10. A method according to claim 9 wherein the substituents are selected from: hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester; optionally substituted amino; carboxamido; or sulfate.

11. A method according to claim 1 or 6 wherein Y is an optionally substituted phenyl group of Formula (ii):



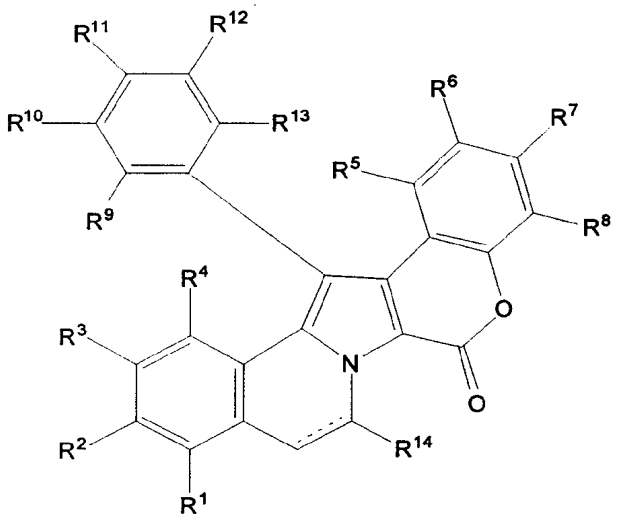
(ii)

Wherein R^9 - R^{13} are as defined for R^1 - R^4 in claim 4.

12. A method according to claim 11 wherein R^9 - R^{13} are independently selected from hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester; optionally substituted amino; carboxamido; or sulfate.

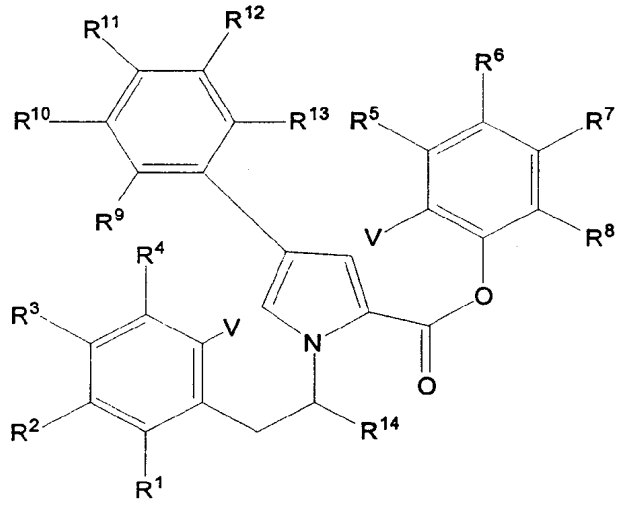
13. A method according to claim 10 wherein R^9 - R^{13} are independently selected from hydrogen, hydroxy, methoxy, ethoxy, iso-propoxy, methyl, ethyl, n-propyl, isopropyl, acetoxy or sulphate.

14. A method of preparing a fused polycyclic pyrrole-containing compound of Formula (IIb):



(IIb)

comprising the step of performing two intramolecular cyclizations on a compound of Formula (Ib):



(Ib)

wherein V is halogen or hydrogen and R^1 - R^{14} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy,

carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano; and
optionally dehydrogenating the cyclized product to form a compound of Formula (Ib) wherein the optional double bond ----- is present.

15. A method according to claim 14 wherein R^1 - R^{14} are independently selected from: hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester; optionally substituted amino; carboxamido; or sulfate, preferably R^1 - R^{13} are independently selected from hydrogen; hydroxy; optionally substituted alkyl, such as methyl, ethyl or propyl; optionally substituted alkyloxy such as methoxy, ethoxy, n-propoxy, iso-propoxy; acyloxy such as acetoxy; or sulfate and R14 is preferably hydrogen or hydroxy and V is bromine, iodine or hydrogen.

16. A method according to claim 1 or 6 wherein U, as defined in Z, is selected from one of CH_2, NH or oxygen, preferably oxygen, and n + o = 0, 1, 2, 3 or 4, preferably 0.

17. A method according to claim 1 or 6 or 14 wherein wherein each V is independently hydrogen, bromine or iodine.

18. A method according to claim 1 wherein V is hydrogen, and the cyclization occurs under oxidative conditions.

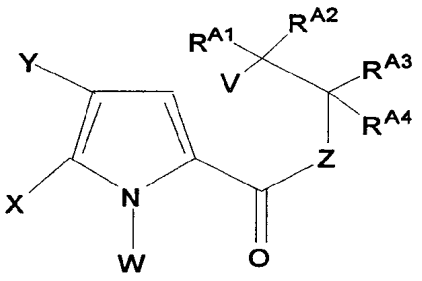
19. A method according to claim 1 wherein V is a halogen atom, preferably bromine or iodine, and the cyclization occurs via the the generation of a radical of Formula (I).

20. A method according to claim 1 wherein V is a halogen atom, preferably bromine or iodine, and the cyclization occurs via a Pd[0]-catalyzed process.

21. A method according to claim 6 or claim 14 wherein both V are halogen, preferably bromine or iodine, and the two cyclizations are performed in one pot.

22. A method according to claim 21 wherein the one pot double cyclization is Pd[0]-catalyzed.

23. A compound of Formula (I):



(I)

wherein:

R^{A1-A4} are each independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano; or

R^{A2} and R^{A3} may optionally together form a bond and R^{A1} and R^{A4} are as defined above or together with the carbon atoms to which they are attached form an optionally substituted carbocyclic or heterocyclic group; or

R^{A2} and R^{A3}, together with the carbon atoms to which they are attached form an optionally substituted saturated or unsaturated carbocyclic or heterocyclic group; or

$R^{A1}R^{A2}C\text{-}CR^{A3}R^{A4}$ forms an optionally substituted aryl group or aromatic heterocyclic group;

Y is selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino,

optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano;

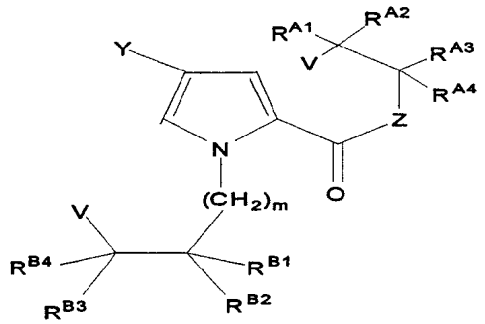
W and X are as defined for Y, or together with the nitrogen and carbon atoms to which they are attached, form a saturated or unsaturated nitrogen containing heterocyclic group which may be optionally substituted or optionally fused to a saturated or unsaturated carbocyclic group, aryl group or heterocyclic group;

V represents a halogen or hydrogen atom;

Z is $-(CH_2)_n-U-(CH_2)_o-$ where U is selected from CH_2, NH or a heteroatom, and n and o are independently selected from 0, 1, 2 or 3.

24. A compound according to claim 23 wherein W and X are as defined in any one of claims 2 to 5.

25. A compound compound of Formula (Ia):



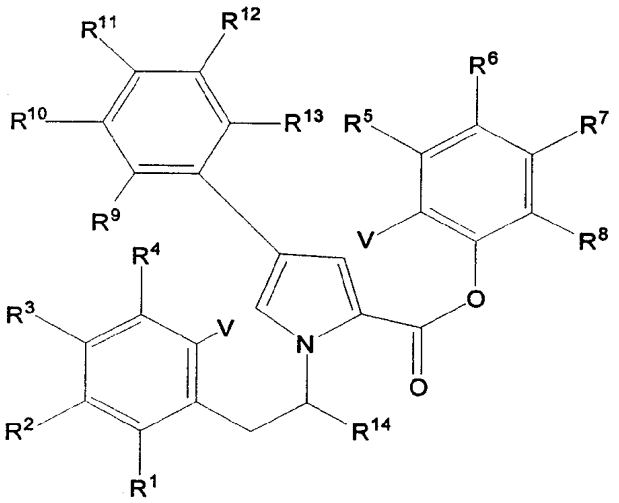
(Ia)

wherein:

R^{A1-A4}, R^{B1-B4}, V, Y, Z and m are as defined in claim 6.

26. A compound according to claim 23 or 25 wherein $R^{A1}R^{A2}C\text{-}CR^{A3}R^{A4}$ forms an optionally subsituted benzene group.

27. A compound of Formula (Ib):



(Ib)

wherein R^{1-14} are independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally protected hydroxy, optionally substituted amino, optionally substituted alkoxy, optionally substituted alkenoxy, optionally substituted alkynoxy, optionally substituted aryl, optionally substituted heterocyclyl, carboxy, carboxy ester, carboxamido, acyl, acyloxy, mercapto, optionally substituted alkylthio, halogen, nitro, sulfate, phosphate and cyano; and

V is halogen or hydrogen.

28. A compound according to claim 27 wherein R^1 - R^{14} are independently selected from: hydrogen; hydroxy; optionally substituted alkyl; optionally substituted alkyloxy; acyloxy; carboxy; carboxy ester; optionally substituted amino; carboxamido; or sulfate, preferably R^1 - R^{13} are independently selected from hydrogen; hydroxy; optionally substituted alkyl, such as methyl, ethyl or propyl; optionally substituted alkyloxy such as methoxy, ethoxy, n-propoxy, iso-propoxy; acyloxy such as acetoxy;

or sulfate and R^{14} is preferably hydrogen or hydroxy; and V is bromine, iodine or hydrogen.

29. A method for the treatment of multidrug resistant tumours comprising the administration of a treatment effective amount of a compound of Formula (II), (IIa) or (IIb), according to any one of claims 1, 6 or 14 as prepared by the methods described herein, to an animal, including a human, in need thereof.

30. Use of a compound of Formula (II), (IIa) or (IIb), according to any one of claims 1, 6 or 14 as prepared by the methods described herein, in the manufacture of a medicament for the treatment of multidrug resistant tumour.

31. An agent for treating multidrug resistant tumours comprising a compound of Formula (II), (IIa) or (IIb), according to any one of claims 1, 6 or 14 as prepared by the methods described herein.

32. A composition for treating multidrug resistant tumours comprising a compound of Formula (II), (IIa) or (IIb), according to any one of claims 1, 6 or 14 as prepared by the methods described herein, together with a pharmaceutically acceptable carrier, diluent or excipient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00516

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C07D 491/14, 207/34, A61K 31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN sub-structure search; MEDLINE, WPIDS, HCA (key-words# cyclisation; cyclization; Paladium; Pd; Pyrrol; lamellarin)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Chemical Abstracts 130:282331, "Synthesis of an Fmoc N-methyl 1H-pyrrole amino acid pentafluoro-phenol ester", & Synth. Commun.(1999), 29(6), 943-949 See compound disclosed RN:222637-47-0	23-24
X	Chemical Abstracts 129:302520, "Synthesis of indolizine amide derivatives", & Nanjing Daxue Xuebao, Ziran Kexue (1998), 34(4), 483-489 See compound disclosed RN:214604-14-5	23-24
X	Chemical Abstracts 129:41035, "Preparation and use of novel (s)-beta-chlorodifluoromethyl-beta-propiolactone as a chiral fluorinated building block", & Tetarahedron (1998), 54(21) 5523-5530 See compound disclosed RN:208248-59-3	23-24

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
3 August 1999

Date of mailing of the international search report
-6 AUG 1999

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00516

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts 126:277429, "Anti-fungal estrogen-like imidazoles. Synthesis and anti-fungal activities of thienyl and 1H-pyrrolyl derivatives of 1-aryl-2-(1H-imidazol-1-yl) ethane", & Eur. J. Med. Chem. (1997), 32(2), 143-149 See compound disclosed RN:188848-30-8	23-24
X	Chemical Abstracts 126:263906, "Facile synthesis of (s)-beta-hydroxy-beta-trichloromethyl aromatic ketones by the regioselective ring cleavage of chiral beta-trichloromethyl-beta-propiolactone under Friedel-Crafts conditions", & Tetrahedron Lett. (1997), 38(9), 1593-1596 See compound disclosed RN"188854-69-5	23-24
X	Chemical Abstracts 112:7428, "Studies on gastric antiulcer active agents.III. Synthesis of 1-substituted 4-(5-tetrazolyl)thio-1-butanones and related compounds", & Chem.Pharm.Bull (1989), 37(4), 958-61 See compound disclosed RN:21187-88-2	23-24
X	Brimble Margaret A., Brimble Mark T., Hodges Richard, Lane Geoffrey A., "Synthesis of 2-Methylpyrrolo[1,2-a]pyrazine-1(2H)-one", Aust.J. Chem (1988), 41(10),1583-90. See compound disclosed RN:123257-04-5, and its Lewis-acid-catalyzed cyclization to 6-methyl-1H-pyrrolo[2,3-c]pyridine-7(6H)-one (II).	1, 23-24
X	Chemical Abstracts 81:63432, "Nitropyrrole derivatives with antimicrobial activity", & Eur.J.Med.Chem - Chim.Ther. (1974) 9(1), 76-80. See compounds disclosed RN:21187-88-2, 53391-44-9, 53391-45-0, 53391-51-8	23-24
X	Chemical Abstracts 80:422, "Pyrrole antibacterial agents II. 4,5-Dihalopyrrole-2-carboxylic acid derivatives", & J.Med.Chem. (1973), 16(11), 1300-2 See compounds disclosed RN:50371-48-7, 50371-62-5, 50371-73-8, 50371-74-9, 50371-75-0, 50371-76-1	23-24
X	Chemical Abstracts 75:129595, "Cyclopropyl 2-pyrrolyl ketone", & J.Org.Chem (1971), 36(19), 2897-8. See compounds disclosed RN:21187-88-2	23-24
X	US, A, 3963480 (Denis M. Bailey) 15 June 1976 See whole document, in particular columns 1, and 3	23-24
X	US, A, 4046775 (Denis M. Bailey) 6 September 1977 See whole document, in particular columns 1-3	23-24
X	FR, 1592066 (Rhone-Poulenc) 19 June 1970 (& GB 1175921 col.2 lines 53-58)	23-24
X	US, A, 3407199 (Irwin J. Pachter) 22 October 1968 See whole documents in particular columns 1-3, Formula 1A	23-24
X	Chemical Abstracts 110:213158, "Synthetic study of indoles and related compounds. Part XIX. A new synthesis of eupolauramine from a benz[f] indole derivative.", & Chem.Pharm.Bull.(1988), 36(9), 3732-5 See compound of formula II.	23-24
	Dale L. Boger, et.al., "Total Synthese of Ningalin A, Lamellarin O, Lukinol A, and Permethyl Storniamide A Utilizing Heterocyclic Azadiene Diels-Alder Reactions",	

AUSTRALIAN PATENT OFFICE
SEARCH REPORT

International application No.
PCT/AU 99/00516

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. Am. Chem. Soc, 1999, 121(1), 54-62, (19 December 1998) See column 4, Reaction Scheme 2.	1-22
X	Heim A. et.al., "Biomimetic Synthesis of Lamellarin G Trimethyl Ether" Angew.Chem.Int.Ed.Engl. 1997, 36, No.1/2, 155-156 See in particular p.155 column 2 lines 1-7	1-22

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 99/00516

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	3963480	US	4046775	US	4084051		
US	4046775	US	3963480	US	4084051		
FR	1592066	BE	710476	CH	481102	CS	149609
		CS	149610	DE	1695667	ES	350291
		GB	1175921	IL	29432	LU	55425
		NL	6801428	NO	127578	SE	333930
		SU	376943	YU	277/68	YU	31811
US	3407199	DE	1670622	FR	6239	GB	1165393

END OF ANNEX

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 99/00516

Patent Document Cited in Search Report	Patent Family Member

END OF ANNEX